EVALUATION OF METHYL ISOTHIOCYANATE AS A TOXIC AIR CONTAMINANT

Executive Summary

Including the Findings of the Office of Environmental Health Hazard Assessment,
the Findings of the Scientific Review Panel, and
the Director's Proposed Decision to List Methyl Isothiocyanate
as a Toxic Air Contaminant

California Environmental Protection Agency
Sacramento, California

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State of California
Department of Pesticide Regulation

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Introduction

Assembly Bills 1807 and 3219 created Article 1.5, Sections 14021 - 14027 of the Food and Agricultural Code, which established a procedure for identification and control of toxic air contaminants (TACs) in California. The statute defines toxic air contaminants as air pollutants that may cause or contribute to an increase in mortality or in serious illness, or that may pose a present or potential hazard to human health. The Department of Pesticide Regulation's (DPR) TAC program focuses on the evaluation and control of pesticides in ambient community air. The program consists of two components: risk assessment (evaluation and identification) and risk management (control and mitigation). Risk assessment is the systematic scientific characterization of potential adverse health effects resulting from human exposures to hazardous agents or situations. This type of assessment includes qualitative information on the strength of the evidence and the nature of the outcomes, quantitative assessment of the exposure and the potential magnitude of the risks, and a description of the uncertainties in the conclusions and estimates. Risk management refers to the process by which policy actions are chosen to deal with the hazards identified in the risk assessment process. Risk managers consider scientific evidence and risk estimates, along with statutory, engineering, economic, social, and political factors, in evaluating alternative regulatory options and choosing among those options.

This report describes the evaluation and risk assessment of methyl isothiocyanate (MITC). In preparing this report, DPR staff reviewed pertinent scientific literature and reports through Summer 2001. Based on the results of this comprehensive evaluation, the Director of DPR will determine whether the MITC is a TAC.

If MITC is designated a TAC, the risk management provisions of the law mandate the DPR to determine the need for and develop appropriate control measures for MITC uses—in consultation with the Office of Environmental Health Hazard Assessment (OEHHA), the Air Resources Board (ARB), the air pollution districts, air quality management districts, and county agricultural commissioners of the affected counties.

What is contained in this report?

This report evaluates the potential for the primary breakdown product of metam sodium, MITC, to be a TAC and includes:

- a review of the available scientific evidence on MITC and other breakdown products regarding their physical properties, sources in the environment, and fate in the environment;
- results documenting ambient airborne concentrations of MITC associated with applications of its parent compound, metam-sodium;
- an estimate of human exposure to MITC in air;
- an assessment of the risk to humans resulting from current or anticipated exposures to airborne MITC and other breakdown products of metam sodium.

What is MITC, what are the primary sources of MITC in the environment, and how is it used?

MITC is the active principle of three other pesticides: the soil fumigants metam-sodium, metam-potassium, and dazomet. On contact with warm, moist soil, metam-sodium, metam-potassium, and dazomet decompose quickly to MITC and other volatile gases, which diffuse upward through the spaces in the soil, and account for the fumigant activity of these soil sterilants. Metam-sodium has been widely used for production agriculture in California, and dazomet and metam-potassium use is increasing. MITC is a general biocide used to control weeds, nematodes, and soil and wood fungi. Although MITC is no longer registered for use in production agriculture in California, two liquid formulations are registered for use as wood treatments.

MITC forms colorless crystals with a pungent horseradish-like odor and is formulated as an emulsifiable concentrate. The molecular formula is C_2H_3NS, and the molecular weight is 73.11. It is highly volatile with a vapor pressure of 16.0 mmHg at 25 °C and a Henry's Law Constant of 2.4×10^{-4} atm·m^3/mol at 20°C. It is soluble in water at 8.2 ppm (at 20°C), and readily soluble in most organic solvents.

MITC was once used as a pre-plant fumigant and along roadsides and other rights-of-way as a weed control agent. However, as of December 1994, it is no longer registered for agricultural or rights-of-way use in California. As of July 2001, two MITC-containing

products are registered for use in California; both are registered for use as wood preservatives and remedial treatments for the control of interior decay in large structural timbers.

The primary source of MITC in the environment is from the breakdown of the widely used fumigant metam-sodium. Metam-sodium is a colorless crystalline dihydrate with a molecular formula of $C_2H_4NNaS_2$ and a molecular weight of 129.18. It is non-volatile, and soluble in water at 9.63×10^{-4} ppm (at 25°C), moderately soluble in methanol, and ethanol, and practically insoluble in most other organic solvents. Metam-sodium is formulated as a water-soluble concentrate or in aqueous solution. It is also available as a water-soluble, surface-active formulation in combination with dichlobenil for use as a non-systemic foaming herbicide to rid sewer lines and drain systems of roots and other organic material.

Metam-sodium has three major uses: it is an agricultural fumigant, a wood preservative, and a root control compound for use in drains and sewers. As a pre-plant soil fumigant, metam-sodium controls soil-borne disease-causing fungi and other organisms, and a variety of annual weeds and grasses. When used as a wood preservative, it arrests internal decay and controls insects in Douglas fir, Western red cedar, and Southern pine poles, and structural timbers such as those used in waterfront structures. As a foaming, non-systemic herbicide, metam-sodium rids sewer lines and drain systems of roots and other organic material. MITC, the principle breakdown product, accounts for the fumigant activity of metam-sodium. As of July 2001, twenty-four metam-sodium-containing pesticides are registered for use in California.

While metam-sodium is used on a wide variety of commodities, most of the metam-sodium applied annually from 1990 through 1998 was used to fumigate soil prior to planting carrots, tomatoes, potatoes, and cotton. In California, use has increased since 1990. Historically, two peak periods of use occur. The first and heaviest occurs during late-winter/early-spring in Fresno County, and is primarily associated with soil pre-plant treatments before planting tomatoes. The second peak use period occurs during mid-summer through early fall in Kern and Imperial counties prior to planting carrots. The amount of metam-sodium used in California has steadily increased in recent years, from an average of 5.5 million pounds in 1990 and 1991, to nearly 15 million pounds in 1998.

Another source of MITC in the environment is from the breakdown of the pesticide dazomet. It has a molecular formula of $C_5H_{10}N_2S_2$ and a molecular weight of 162.28. As

of July 2001, nineteen dazomet-containing products are registered for use in California. Dazomet is mainly used as a slimicide in pulp and paper manufacture and as a microbiocide in water-cooling tower systems. However, one product is registered for use as a pre-plant soil fumigant. Applied directly to moist soil, it decomposes quickly to several compounds, including MITC, which diffuses upward through the spaces in the soil, and accounts for the fumigant activity.

A third source of MITC in the environment is from the breakdown of the pesticide metam-potassium. As of July 2001, eighteen metam-potassium-containing pesticides were registered for use in California. In California, metam-potassium is mainly used as an antifoulant for water-cooling systems, condensers, and similar equipment. While two metam-potassium products have recently been registered for use as a soil fumigant in California, its current use in that regard is minimal and not widespread.

The annual use of dazomet and metam-potassium in California are relatively insignificant when compared to that of metam-sodium; nearly 15 million pounds of metam-sodium were reported used in 1998 contrasted with less than 16,000 pounds of dazomet, less than 9,200 pounds of metam-potassium, and less than 200 pounds of MITC used that same year. Therefore, this report focuses primarily on the relationship between metam-sodium and MITC, the transformation of metam-sodium into MITC and its subsequent fate in the environment, and monitoring studies conducted in California to measure the airborne concentrations of MITC following agricultural applications of metam-sodium.

What are the fates of metam-sodium, dazomet, metam-potassium, and MITC in the environment?

In the agricultural setting, metam-sodium is applied directly into or onto the soil prior to planting. Once applied to the soil, its rapid and complete breakdown results in a soil solution containing mainly MITC. In the soil environment, the conversion of metam-sodium to MITC occurs usually within one hour to one day following application, follows first-order kinetics, and occurs with efficiencies ranging from 87 to 95 percent. The decomposition rate depends strongly on soil temperature, soil composition, and soil moisture. Warm soil temperature, increase in clay or organic material content, small soil particle size, and low soil moisture facilitate the rapid conversion of metam-sodium to MITC. When used as a soil fumigant, metam-potassium decomposes to release MITC following a similar pattern.

In the soil, dazomet decomposes rapidly to form MITC, formaldehyde, hydrogen sulfide, and monomethylamine. It is this combination of volatile gases that results in the fumigant activity. The decomposition of dazomet can occur in as little as 10 to 15 minutes. Soil moisture may be the key factor in dazomet decomposition. However, soil temperature, pH, moisture content, and soil type all have an affect on the rate of degradation. Warm soil temperatures and increased soil moisture content (up to approximately 80% of soil saturation) facilitate the decomposition of dazomet.

MITC leaves the soil primarily due to volatilization. Specific factors affect the volatilization rate of MITC from soils treated with metam-sodium or dazomet. In order of importance, these factors include: soil temperature, soil type, soil pH, and soil moisture content. Warm soil temperatures, clay or sandy-loam soil types, increased soil pH, and lower soil moisture facilitate the volatilization of MITC. In one greenhouse study, MITC was generated at approximately 60 % by weight, when compared to the total amount of metam-sodium injected into the soil. Decomposition also plays a role in the loss of MITC from the soil. Its decomposition in soil follows first-order kinetics and also depends on soil temperature and soil type. Warm temperatures and loamy soils promote decomposition, which reportedly occurs with half-lives ranging from 0.5 to 50 days depending on soil conditions. Intensive, frequent use of metam-sodium may result in adaptation of the soil microorganisms and the enhanced degradation of MITC.

MITC loss from water occurs primarily by hydrolysis. MITC's stability depends on pH, water temperature, and the presence of sediment. The rate of hydrolysis is slow in water but increases significantly in the presence of sediments similar to those found in rivers, ponds, or lake-bottoms. Reported hydrolysis half-lives range from 0.7 to 178 days.

In air, the primary MITC transport and transformational pathway is gas phase photolysis. In general, the persistence of MITC in air depends upon the rate of its photodissociation and the reactivity with OH radical, NO_3 radical, and ozone in the atmosphere. Research suggests that photolytic degradation may be an effective pathway for removal from the atmosphere. In laboratory experiments, using ambient solar radiation, MITC half-lives ranged from 29 to 39 hours. In laboratory experiments, the photodecomposition resulted in the production of methyl isocyanide, methyl isocyanate (MIC), methylamine, N-methyl formamide, sulfur dioxide, hydrogen sulfide, and carbonyl sulfide. Research suggests that MIC may be the major stable photoproduct formed in the atmosphere.

The decomposition of metam-sodium and dazomet results in low concentrations of two other highly volatile decomposition products: hydrogen sulfide (H_2S) and carbon disulfide (CS_2). The dominant reactions of H_2S and CS_2 in the atmosphere are by daytime reaction with the OH radical. Based on the literature rate constants for the reactions of the OH radical with H_2S and CS_2 and using a 24-hr tropospheric average OH radical concentration of 1×10^6 molecule cm^{-3}, then the calculated half-lives of H_2S and CS_2 are 2.5 days and approximately 2 weeks, respectively.

What are the reported air concentrations of MITC in California?

Nine air monitoring studies have been conducted in California to document the airborne concentrations of MITC associated with metam-sodium applications. Current metam-sodium technical information bulletins (TIB), which are part of the label when metam-sodium is used in California, specifically require the soil to be "sealed" immediately following application to minimize off-site movement of odors. Several of these studies were conducted under conditions that meet the current TIB, including three ambient air monitoring studies and two application-site studies. They were used as the basis of the exposure and risk assessments. In 1993, ARB's Engineering and Laboratory Branch conducted an ambient study. In 1998, an ambient study for pesticides, including MITC, was conducted in Lompoc, California to investigate the potential causes of respiratory illnesses in that city. In 1998, Seiber et al. measured the ambient airborne residues of MITC indoor and outdoor air in townships near fields treated with metam-sodium. In 1993, DPR's Environmental Monitoring and Pest Management Branch conducted an application-site study in response to statewide complaints from people living near fields treated with metam-sodium of odor and irritation. In 1999, Merricks measured airborne concentrations of MITC following both sprinkler irrigation and shank injection applications of metam-sodium.

During four other application-site studies conducted in California, the soil was not "sealed" following application, as is currently required. Therefore, the air concentrations measured during these applications may not be representative of current practices. These four studies were included in this report to provide historical perspective. Three application-site studies were conducted by the ARB—two application-site studies in 1993, and a third in 1995. The fourth study was conducted by Rosenheck in 1993 to measure off-site movement of MITC following an application of metam-sodium.

a. Ambient air monitoring studies

DPR and ARB design ambient monitoring studies to measure the concentrations of a particular pesticide in the ambient air during the time and in the region of peak use. Ambient monitoring studies are not associated with a specific application. These studies are designed to provide an estimate of the exposures that people living in proximity to pesticide applications might experience. In general, locations such as schools, fire stations, or other public buildings are selected as the monitoring sites. DPR relies on historical Pesticide Use Report (PUR) data as a means to predict appropriate monitoring seasons and locations.

ARB conducted an ambient monitoring study in Kern County from July 20-30, 1993 to determine the concentrations of MITC present in the ambient air at the time and location of peak use of metam-sodium. Four sites were selected in Kern County near anticipated application areas. Three of these sites were on the rooftops of schools, or school district offices, in the communities of Weed Patch, Lamont, and Shafter. The fourth site was established on the rooftop of the ARB Ambient Monitoring Station in Bakersfield.

ARB began ambient air monitoring on July 20, 1993 and concluded on July 30, 1993. Eighty-eight percent of the sixty-four total samples contained detectable residues of MITC (MDL = less than 0.003 parts per billion (ppb) [< 0.01 $\mu g/m^3$] for a 24-hour sample); positive concentrations ranged from 0.0097 to 6.0 ppb (0.029 to 18 $\mu g/m^3$). According to the 1993 PUR, over 157,000 pounds of metam-sodium were applied in Kern County during the period starting five days prior to the onset of monitoring through the end of the monitoring study. Applications occurred at distances ranging from less than one mile to about twelve miles from the nearest monitoring stations.

In the late summer of 1998, an ambient air monitoring study for pesticides, including MITC, was conducted to investigate the potential causes of respiratory illnesses in Lompoc, California. The MITC ambient air samples were collected from on August 31, 1998, and then continuously from September 9-13, 1998. Samples were collected at five locations within the city limits near the ag-urban interface. Sixty duplicate samples were collected. Twenty-three percent of the samples collected contained detectable levels of MITC. The concentrations ranged from "not detected" to 0.34 ppb (1.0 $\mu g/m^3$). No detection limit or quantitation limit was provided. Higher concentrations were detected during nighttime hours, compared to daylight hours.

A recent study was conducted to monitor airborne concentrations of MITC near Kern County applications of metam-sodium during two monitoring periods; the first period was during the summer of 1997 and the second period was during the winter of 1998. Samples of both outdoor and indoor air in three towns were collected during the summer monitoring period—Shafter, Lamont, and Weedpatch. During the wintertime, indoor and outdoor air samples were collected in Lamont, Weedpatch, and Arvin. For the summer samples, the number of measurable residues was greatest during the months of May through July, with some of the highest residues occurring during June and July. For the winter samples, the greatest number of measurable levels and the greatest residue levels occurred in January. Detectable concentrations were measured in both indoor (residential) and outdoor air, with the highest concentrations occurring in outdoor air during the summer months, when warm, dry temperatures, and the increased use of metam-sodium occur. It is interesting to note that indoor residential air concentrations were similar in magnitude (and sometimes exceeded) outdoor concentrations, both during the summer and winter studies. Proximity to the treated fields and prevailing wind directions seemed to be the contributing factors with respect to detected ambient concentrations.

From May through August 1997, 208/34/96 (indoor/outdoor house/ambient) duplicate samples were collected, for a total of 416/68/192 (indoor/outdoor house/ambient) samples. Duplicate samples were averaged, and the reported concentrations ranged from <LOQ to 18.00 µg/m³ (<LOQ to 6.02 ppb) for the indoor samples, from <LOQ to 10.60 µg/m³ (<LOQ to 3.55 ppb) for the outdoor house samples, and from <LOQ to 31.10 µg/m³ (<LOQ to 10.41 ppb) for the outdoor ambient samples. The limit of quantitation (LOQ) was ~55 ng/sample or 6.2×10^{-2} µg/m³ (2.1×10^{-2} ppb) for a 12-hour sample collected at a sampling rate of about 1.2 L/min. Over 75 percent of the samples collected during the summer of 1997 had measurable concentrations of MITC.

In January and March 1998, 68/67/44 (indoor/outdoor house/ambient) duplicate samples were collected, for a total of 136/134/88 (indoor/outdoor house/ambient) samples. Duplicate samples were averaged, and the reported concentrations ranged from <LOQ to 3.69 µg/m³ (<LOQ to 1.23 ppb) for the indoor samples, from <LOQ to 4.53 µg/m³ (<LOQ to 1.52 ppb) for the outdoor house samples, and from <LOQ to 4.06 µg/m³ (<LOQ to 1.36 ppb) for the outdoor ambient sample. The limit of quantitation (LOQ) was ~55 ng/sample or 6.2×10^{-2} µg/m³ (2.1×10^{-2} ppb) for a 12-hour sample collected at a sampling rate of about 1.2 L/min. Nearly 67 percent of the samples collected in the winter of 1998 had measurable concentrations of MITC.

b. Application-site air monitoring studies

Application-site monitoring studies are conducted to measure the concentrations that are present in the air associated with a specific pesticide application. Generally, application-site studies are conducted at a specific field, where the pesticide is applied at the highest allowed label rates. Six application-site studies were conducted in California to measure the airborne concentrations of MITC following applications of metam-sodium.

Three sprinkler applications were studied. One study, conducted in August 1993, measured the airborne concentrations of MITC associated with a sprinkler application of metam-sodium in Kern County. Sixty-nine percent of the eighty-eight samples collected contained detectable residues of MITC (MDL = 2 ppb [5.95 $\mu g/m^3$] for 12-hr samples). Positive MITC concentrations measured during that study ranged from 2.27 to 2,450 ppb (6.75 to 7,290 $\mu g/m^3$). Information provided to DPR during the preparation of this report indicates the potential of an inversion during the period of the application. The presence of an inversion would be inconsistent with current requirements. However, the ability to determine whether an inversion was present during the application cannot be made. Given this uncertainty, caution should be taken with respect to the air concentrations and other values calculated from the study.

During that application, samples were also collected to measure the levels of H_2S and CS_2. Measurable concentrations of H_2S above the detection limit (3 ppb) were detected up to 21 hours after the start of the application. Because H_2S is a minor breakdown product of metam-sodium, relatively low concentrations were expected to be present as metam-sodium degraded. The highest detected level was 76 ppb and occurred during application indicating that metam-sodium was rapidly degrading, as would be expected given the soil conditions during this study. No detectable residues were found during the watering-in period, and in following sampling periods until the afternoon following application at which time downwind levels ranged from 3 to 8 ppb. Air samples for carbon disulfide were collected at five meters from the edge of the field. All samples were below the laboratory quantification limit of 4 ppb.

The second study measured the concentrations of MITC associated with a sprinkler application of metam-sodium in Kern County in June 1999. Seventy-one percent of the samples collected contained detectable MITC residues (MDL = 0.14 ppb [0.42 $\mu g/m^3$] for

4-hr samples). Positive concentrations ranged from 0.13 to 280 ppb (0.4 to 837 $\mu g/m^3$). However, air samplers were not positioned directly downwind for the entire study duration.

The third study measured the concentrations of MITC associated with a sprinkler application of metam-sodium in Madera County in May 1992. Nearly 100 percent of the 100 samples collected contained detectable concentrations of MITC. Positive MITC concentrations measured during that study ranged from 1.29 to 435 ppb (3.86 to 1,300 $\mu g/m^3$). However, this study was not conducted following current TIB requirements, and the results may not be representative of current practices.

Four soil injection applications of metam-sodium were monitored. The first study was conducted in Kern County in June 1999. Measurable MITC residues were detected in eighty-nine percent of the samples (MDL = 0.14 ppb [0.42 $\mu g/m^3$] for 4-hr samples). Positive MITC concentrations ranged from 0.13 to 281 ppb (0.4 to 840 $\mu g/m^3$). However, air samplers were not positioned directly downwind for the entire study duration.

Three other soil application studies were conducted, however, the applications monitored during these studies did not comply with the requirements of the current TIB, and therefore may not be representative of current practices. The first study measured the air concentrations of MITC and MIC associated with an application of metam-sodium in Kern County in August 1995. Measurable residues were detected in 100 percent of the samples collected—thirty-three total MITC samples and thirty-five total MIC samples—(MDL_{MITC} = 0.03 ppb [0.088 $\mu g/m^3$] for a 12-hour sample; MDL_{MIC} = 0.005 ppb [0.015 $\mu g/m^3$] for a 12-hour sample). The positive MITC concentrations ranged from 0.21 to 84 ppb (0.24 to 250 $\mu g/m^3$). MIC sample concentrations ranged from 0.09 to 2.5 ppb (0.2 to 5.8 $\mu g/m^3$).

The second study was conducted in Contra Costa County in March 1993. Measurable concentrations of MITC were detected in eighty-eight percent of the forty-eight samples collected (MDL = 0.017 ppb [0.054 $\mu g/m^3$] for a 12-hour sample). The positive MITC concentrations ranged from 0.017 to 81.0 ppb (0.051 to 242 $\mu g/m^3$).

The final study was conducted in Kern County during July 1993. Measurable residues were detected in 100 percent of the seventy-two samples collected during this study

(MDL = 0.007 ppb [0.021 µg/m^3] for a 12-hour sample). The positive MITC concentrations ranged from 1.1 to 270 ppb (3.2 to 880 µg/m^3).

What are the expected exposures to airborne concentrations of MITC, and when do these exposures occur?

Short term and moderate term exposures of the general population to airborne MITC were estimated from monitoring studies conducted under both "ambient" and "application site" scenarios.

Ambient MITC exposures were those occurring during the time and in the region of peak metam sodium use. They were not, however, related to a specific application. Three separate ambient exposure studies were examined for this report. Two of these were conducted in Kern County, while the third was conducted in Lompoc. Short term estimates, which were used to evaluate potential acute risk and which included 1-, 8-, and 24-hour values, ranged between 0.1 and 14.6 ppb. Moderate term estimates (amortized), which were used to evaluate potential seasonal risk, ranged between 0.0006-3.54 ppb.

Application site exposures were those which can potentially occur to individuals situated near to a field during a specific metam sodium application, usually at the highest label-approved rate. A total of seven California application site studies were considered for this report. These included 4 soil injection studies and 3 fixed-set sprinkler studies done under cool and warm air / soil conditions. The short term estimates (amortized) ranged between 15 and 2853 ppb for 1-hour exposures, between 8.3 and 2348 ppb for 8-hour exposures, and between 0.08 and 1102 ppb for 24-hour exposures. The moderate term estimates ranged between 0.38 and 80 ppb depending on site and distance from the application.

What are the potential acute and seasonal health effects of MITC?

MITC is a strong ocular and respiratory tract irritant. This was evident in the experience of residents of the Dunsmuir area, who were exposed to airborne MITC after the July 1991 metam-sodium spill into the Sacramento River. It was also evident among residents of Earlimart, CA, who were exposed to MITC in November 1999 after an illegally conducted metam sodium sprinkler application resulted in the movement of an airborne plume of MITC over the town. Finally, eye, respiratory, and skin irritation complaints

have been prominent among case reports of the California Pesticide Illness Surveillance Program. Systemic problems (*eg.*, nausea, dizziness, headache, etc.) have also been documented after purported MITC exposures. Longer term disabilities such as reactive airways dysfunction syndrome (RADS) may be induced by short term inhalation exposure to MITC, though the evidence for this is not conclusive.

Eye irritation, detected as statistically significant increases in perception of irritation and in eyeblink rate, was documented at air concentrations as low as 800 ppb in human volunteers exposed through specially-fitted goggles (*Note*: As the volunteers were exposed only through the eyes, the potential for adverse impacts in the respiratory system was not evaluated in this study.). The resultant no observed effect level (NOEL) of 220 ppb was the critical NOEL used for evaluation of potential short term human exposure to airborne MITC.

In addition to these human studies, animal studies have also illustrated both the acute systemic toxicity and irritative capacity of MITC. Acute oral gavage exposure in rats between 25 and 300 mg/kg led to sedation, dyspnea, altered body positions, ruffled fur, crying, spasms and exophthalmos. The LD_{50} in that study was 55 mg/kg in females (F) and 82 mg/kg in males (M). Similar clinical signs were noted upon dermal exposure of rats at a dose range of 60-600 mg/kg (LD_{50} = 181 [F] and 225 [M] mg/kg) and rabbits at a dose range of 50-300 mg/kg (LD_{50} = 202 [F] and 145 [M] mg/kg). Finally, studies in rabbits confirm that MITC is a powerful irritant both to skin and eyes.

Acute inhalation studies in animals have yielded conflicting results, but do identify a potentially very damaging route of exposure. The most reliable studies in Sprague-Dawley rats show a 1-hour LC_{50} of 633 ppm and a 4-hour LC_{50} of 180 ppm. Clinical signs in the former study included hyperactivity followed by hypoactivity, eye irritation, dyspnea and convulsions.

Subchronic toxicity was evident in the critical 4-week Wistar rat inhalation study, which was conducted according to a 6-hours/day, 5-days/week exposure regimen. This study established a LOEL at the low dose of 1.7 ppm based on evidence of nasal epithelial atrophy at that dose. Signs and symptoms at the intermediate dose of 6.8 ppm included nasal epithelial atrophy, a rise in polymorphonuclear granulocytes (considered evidence for sub-histopathologic lung damage), and clinical signs. The latter, which were of unclear toxicologic significance, included somnolence, eye closure, and ruffled fur. Markedly more severe signs of respiratory tree irritation, including bronchopneumonia,

emphysema, bronchial and tracheal epithelial proliferation, rhinitis, and focal metaplasia of the nasal passages, in addition to nasal epithelial atrophy, increases in lung weight, and decreases in body weight, were observed at the high dose of 34 ppm. Haber's Law was invoked to convert the 6-hours/day, 5-days/week exposure regimen to 24 hours/day, 7 days/week, resulting in a LOEL of 300 ppb. An uncertainty factor of 3 was then imposed to calculate an estimated critical subchronic NOEL of 100 ppb. This value was used to evaluate risks associated with seasonal exposure to MITC.

Oral exposure of rats over a 3-month period produced a LOEL of 2 mg/kg/day based on stomach lesions, liver inflammation, spermatogenic disturbance, and alteration in adrenal and ovary weights. These effects were considered slight at that dose, but increased in severity at 10 and 40 mg/kg/day. A NOEL of 0.7 mg/kg/day was established in a 3-month mouse oral gavage study based on reduced body weight gain and increased liver weights at 1 mg/kg/day. At higher doses, toxic effects included thickening of the forestomach lining, inflammation of the liver, testicular / spermatogenic disturbances and decreased ovary weights.

No chronic inhalation toxicity studies were available for MITC. NOELs for chronic oral studies in the rat, mouse and dog were based on decreased body weight and water/food consumption, and poor general condition.

Is there any potential cancer risk from exposure to MITC?

The 2-year rat drinking water study provided evidence that MITC may have induced mammary fibroadenomas and carcinomas in females. A small increase in subcutaneous fibromas was also noted at the high dose, though it was unclear if MITC was responsible for the rise. The 2-year mouse drinking water study provided evidence that MITC may have induced cutaneous fibrosarcomas in both sexes. However, the data from neither long-term drinking water study were sufficient to trigger a quantitative oncogenic risk evaluation.

Does the concentration of MITC in ambient air pose a potential health hazard for humans?

Risk characterization for non-oncogenic endpoints requires knowledge of the toxicity endpoints and the expected exposures. Monitoring of MITC levels under ambient and

application site scenarios demonstrated the potential for exposure of the general public. The risk of incurring adverse effects from these exposures is expressed as the margin of exposure (MOE), defined as the ratio of the NOEL value established in animal or human studies over the human exposure level. Generally, a MOE of >100, which takes into account the possibility of 10-fold variations in susceptibility within the human population as well as between laboratory animals and humans, is considered adequate to protect humans from the effects in question. A MOE of >10 is sufficient if the toxicity endpoints are derived from human data. Exposure scenarios resulting in MOEs lower than these values will be considered during the risk management process.

Using the critical acute NOEL of 220 ppb established in a human eye irritation study and the estimates indicated above for the short term ambient exposure levels, acute ambient MOEs ranged between 15 and 2200. Because the MOEs did not drop below 10, a human health risk was not indicated under these conditions. However, under the short term application site exposure scenarios, the MOEs for 1-, 8-, and 24-hour exposures were <1 to 5, <1 to 7, and <1 to 17, respectively, indicating a potential human health risk.

Combining the critical estimated subchronic NOEL of 100 ppb established in the 4-week rat inhalation study and the estimates indicated above for the moderate term ambient exposure levels, mean seasonal ambient MOEs were found to range between 28 and 166,667 ppb. MOEs for three seasonal ambient determinations, at Weedpatch in 1993 and 1997 and at Lamont in 1993, were below the benchmark of 100 for protection of human health. Under moderate term application site exposure scenarios, the MOEs ranged between 1-50, signifying a potential seasonal human health risk in all cases.

The Reference Exposure Level (REL) is defined by the Office of Environmental Health Hazard Assessment as "the concentration level at or below which no adverse health effects are anticipated for a specified exposure duration". REL determinations are based on the best available medical and toxicological studies and "are designed to protect the most sensitive individuals in the population by the inclusion of margins of safety". The REL for acute effects of MITC was calculated by dividing the critical NOEL, 220 ppb, by 10 to account for intrahuman variability when the NOEL was determined in a human study. Because the eye irritation NOEL was stable at 1, 4 and 8 hours in the critical laboratory study, the REL was relevant for potential exposure times of up to 8 hours. The resultant value, 22 ppb, was well below the anticipated acute exposure levels established in the application site air monitoring studies (41-2853 ppb for 1-hour exposures and 32-2348 ppb for 8-hour exposures), indicating a potential human health hazard. As noted

above, 1-, 8-, and 24-hour ambient exposure estimates did not exceed 14.6 ppb. A human health concern was therefore not indicated under ambient conditions.

The subchronic REL of 1 ppb was generated by dividing the 24-hour critical estimated subchronic rat inhalation NOEL of 100 ppb by an uncertainty factor of 100 (10-fold to account for intrahuman variability and 10-fold for the assumption that humans are more sensitive than animals). Seasonal ambient time-weighted average MITC concentration determinations (range: 0.0006-3.54 ppb) indicated some cause for human health concern. A health concern clearly existed for application site scenarios (range: 0.38-80 ppb) where the REL values were almost always exceeded.

A chronic REL value was estimated in the eventuality that use patterns or air monitoring at some future time would indicate a potential for chronic exposure. In the absence of a chronic inhalation toxicity study, the 24-hour chronic REL was estimated by dividing the subchronic REL by a default uncertainty factor of 10, yielding a value of 0.1 ppb. Chronic exposure levels were not available in this document to determine whether or not a chronic health concern exists.

Do any of the other metam sodium degradation products pose a potential health hazard?

Human exposure to methyl isocyanate (MIC) may occur following metam-sodium applications due to photolysis of the metam-sodium breakdown product MITC. In laboratory experiments, the yield of MIC from MITC has been reported to be about 7 percent. The experiments were performed using filtered laboratory air and sealed Tedlar, borosilicate, or quartz containers and artificial light. Under normal environmental conditions, the degree of conversion may be different. A monitoring study in which MIC levels were measured following applications of metam-sodium revealed that MIC levels were as high as 2.5 ppb, 4% of the MITC levels.

MIC is known to be highly reactive and acutely toxic to man and animals. Acute symptoms following exposure to high air concentrations of MIC include asthma, chest pain, pulmonary edema, dyspnea, respiratory failure, skin and eye injuries, and death. An accidental release of MIC in Bhopal, India in 1984 caused the deaths of up to 5000 people within a few days. No direct evidence was found to suggest that MIC causes pulmonary sensitization. However, other isocyanates do induce pulmonary sensitization;

subsequent exposure to extremely low airborne concentrations (ppb) can cause asthmatic episodes. The 6-hr inhalation LC_{50} for MIC was 6100 ppb (14 mg/m^3) in rats, 12,200 ppb (28 mg/m^3) in mice and 5400 ppb (12 mg/m^3) in guinea pigs. A conditional acute REL value of 1 ppb was set based on a study of eye irritation potential in humans, indicating a possible cause for concern under field conditions (as noted, limited monitoring indicated that MIC levels rose as high as 2.5 ppb). The US OSHA 8-hour permissible exposure limit (PEL) is 20 ppb. The Cal OSHA PEL is also 20 ppb.

Little information on the toxic effects of long-term (chronic) low level exposure to MIC in humans or animals is available. In a study designed to mimic the conditions of exposure around the 1984 MIC disaster in Bhopal, India, a single 2-hr exposure of rats and mice *via* inhalation to MIC (followed by 2 years of observation) led to intraluminal fibrosis of lung secondary bronchi in rats at the high dose of 10 ppm. Male rats had marginally increased rates of pheochromocytomas of the adrenal medulla and adenoma of pancreatic acinar cell. MIC is considered a "Group D" chemical by the US EPA, *i.e.*, not classifiable with respect to human carcinogenicity.

Hydrogen sulfide (H_2S) is formed as part of the same monomolecular cleavage reaction that produces MITC from metam-sodium under dilute aqueous conditions. H_2S disrupts intracellular electron transport by inhibiting cytochrome oxidase. Metabolic acidosis results when the shift from aerobic to anaerobic metabolism occurs, provoking a build-up of lactate. H_2S is also a mucus membrane and respiratory irritant. Death results from respiratory arrest and hypoxia. Symptoms commonly reported after accidental human exposures include dyspnea, sore throat, coughing, chest pain and signs of pulmonary obstruction. Less common symptoms include pulmonary edema, cyanosis and pneumonia. Severe neurologic and cardiovascular effects can be present in those recovering from high-level exposures.

Oil refinery workers exposed subchronically or chronically showed a possible H_2S-related increase in liver toxicity. Respiratory symptoms were evident in children, but not adults, living downwind of two oil refineries. A range of clinical signs, including weight loss, pulmonary, nasal, renal, neurologic and blood signs, were evident in subchronic animal studies. H_2S appeared weakly mutagenic in one *Salmonella* study. The potential for oncogenicity is not known.

The Agency for Toxic Substances and Disease Registry (ATSDR) lists an acute minimum risk level (MRL) of 70 ppb based on respiratory effects (bronchial obstruction)

in humans, and an intermediate duration MRL of 30 ppb based on respiratory effects in mice. The California Ambient Air Quality Standard is also 30 ppb for a 1-hour average. Measurements of H_2S after applications of metam-sodium showed levels reaching 76 ppb at 1 to 4 hours post application, exceeding these standards. However, the occupationally oriented Cal OSHA PEL is 10,000 ppb, with a short-term exposure limit (STEL) of 15,000 ppb.

Human exposure to carbon disulfide (CS_2) may follow metam applications. CS_2 is a degradation product of metam-sodium, particularly under acidic conditions (pH<5). Acute human exposure to CS_2 by inhalation leads to local irritation, pharyngitis, CNS toxicity and death. Oral exposure can also be fatal. Dermal and ocular exposures cause severe burns. CNS, cardiovascular, gastrointestinal and immune toxicity result from CS_2 exposures in humans in the range of 3 to 320 ppm for periods of months to years. Animal studies indicate adverse effects to the kidney as well. Adverse reproductive effects in humans and increased fetal resorptions in rabbits are also possible outcomes of CS_2 exposure. Measurements of CS_2 after applications of metam-sodium showed levels at or below the detection level of 4 ppb. The Cal OSHA PEL is 4 ppm, with a short-term exposure limit of 12 ppm.

Methylamine is produced upon cleavage of metam-sodium or MITC under acidic conditions. This compound is known for its irritant properties to eyes, nose and throat upon brief exposures. Severe exposures may lead to pulmonary edema. One study indicated possible mutagenicity. The OSHA PEL for methylamine is 10 ppm. No monitoring data are available with respect to metam-sodium applications.

Carbonyl sulfide (COS) is produced upon cleavage of MITC in the gut. Acute inhalation exposure can result in fatality due to respiratory paralysis. Sublethal inhalation leads to giddiness, headache, vertigo, amnesia, confusion, unconsciousness, salivation, nausea, vomiting, diarrhea, cardiac arrhythmia, albuminuria, weakness and cramps. Information on subchronic and chronic effects in humans is not currently available, nor is there information on the oncogenicity, genotoxicity or developmental/reproductive toxicity of COS. Regulatory limits for COS have not been established, nor are monitoring data after metam-sodium applications currently available.

Inhalation co-exposure to any combination of MITC, MIC and H_2S, the three major breakdown products of metam sodium, could elicit additive or synergistic effects. These might particularly be expected in respiratory and ocular tissues, which are known to be

sensitive to the irritative effects of these compounds in isolation. Unfortunately, as no clear experimental or epidemiologic data are available to suggest the presence of, or potential for, additive/synergistic interactions, it can only be said at this point that such effects are plausible.

Office of Environmental Health Hazard Assessment

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MEMORANDUM

Winston H. Hickox
Agency Secretary

Gray Davis
Governor

TO: Gary Patterson, Ph.D., Chief
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FROM: Anna M. Fan, Ph.D., Chief
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Melanie Marty, Ph.D., Chief
Air Toxicology and Epidemiology Section

DATE: January 31, 2002

SUBJECT: REVISED FINDINGS ON THE HEALTH EFFECTS OF METHYL ISOTHIOCYANATE

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) provides review, consultation, and comments to the Department of Pesticide Regulation (DPR) on the evaluation of the health effects of pesticides that are candidate toxic air contaminants (TAC). As part of its statutory responsibility, OEHHA also prepares findings on the health effects of the candidate pesticide TACs. These findings are to be included as part of the final DPR report.

Attached you will find a revised version of OEHHA's draft findings on the health effects of methyl isothiocyanate. Our original findings were submitted to DPR in December 1999. Changes to the original draft findings are shown in underlined text. Revisions to our findings were necessary as a result of changes introduced into the draft TAC document by DPR and submitted to OEHHA in August 2001. Note that we have provided comments on the revised draft TAC document in addition to our previous comments on the original draft TAC document dated March 2000.

Our staff would be happy to meet with your staff to discuss these findings. If you have any questions, please contact either one of us at (510) 622-3200 or Dr. David Rice at (916) 324-1277.

Attachment

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Office of Environmental Health Hazard Assessment's Draft Findings on the Health Effects of Methyl Isothiocyanate

Pursuant to Food and Agricultural Code Sections 14022 and 14023, the Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency provided consultation to the Department of Pesticide Regulation (DPR) on the evaluation of health effects of the chemical methyl isothiocyanate (MITC), formed as a degradation product of the pesticide active ingredient metam sodium. Furthermore, OEHHA has reviewed and commented on the draft documents on the evaluation of human health risk associated with potential exposure to MITC for consideration of the identification of MITC as a toxic air contaminant (TAC). As part of its statutory responsibility, OEHHA has prepared these findings on the health effects of MITC which are to be included as part of DPR's draft TAC document.

Environmental Fate and Exposure

1. Metam sodium is used mainly as an agricultural fumigant. After field application in aqueous solution through sprinklers or direct shank injection, it is converted to MITC in soil within the first day. MITC diffuses through soil to produce the pesticidal effects, and a major portion is eventually lost by volatilization to air. The half-life of MITC in air by photolytic decomposition was reported as 29 to 39 hours in natural sunlight.

2. Three ambient air monitoring studies carried out in Kern and Santa Barbara Counties and seven application-site monitoring studies in Contra Costa, Kern and Madera Counties are described in the draft TAC document. Ambient air concentrations of MITC ranged from not detected (less than 0.003 ppb) to 10.4 ppb (31.1 $\mu g/m^3$), averaged over a 12-hour sampling time. Mean time-weighted average (TWA, 24-hour) concentrations of MITC in ambient air ranged from 0.1 to 8.8 ppb (0.3 to 26.4 $\mu g/m^3$). Concentrations of MITC in air at metam application sites were as high as 2,853 ppb (8,490 $\mu g/m^3$) for a one-hour sample. Mean TWA (24-hour) concentrations of MITC in application site air ranged from about 13 to 1,100 ppb (39 to 3,300 $\mu g/m^3$).

3. Two worker exposure studies (one in Washington State and one in Arizona) also provide perspective on MITC concentrations at metam sodium application sites. Mean concentrations of MITC in personal air monitors varied from 29.3 to 504 ppb (88 to 1,500 $\mu g/m^3$).

4. Breakdown of metam sodium in soil or water and MITC in air results in the formation of several other toxic chemicals including methyl isocyanate (MIC), carbon disulfide (CS_2), and hydrogen sulfide (H_2S). Conversion of MITC to MIC in laboratory experiments was about 7 percent, indicating that MIC toxicity could be a concern in areas of elevated MITC concentrations. Concentrations of these chemicals in air were not usually monitored in the metam sodium/MITC studies. However, in one study in Kern County, measured application-site levels of MIC in 12-hour collections ranged from 0.09 to 2.5 ppb (0.2 to 5.8 $\mu g/m^3$), when MITC concentrations ranged from 0.08 to 84 ppb (0.24 to 250 $\mu g/m^3$). MIC half-life in air was not reported, but is probably less than one day.

5. Human exposure to atmospheric MITC can occur by both inhalation and dermal routes, but the predominant exposure route for systemic doses is inhalation. Inhalation uptake is assumed to be 100 percent for these estimates, based on the physical properties of MITC.

6. Dermal uptake of MITC has not been quantitatively estimated in these studies; it would be likely to provide less than 1 percent of the systemic dose received by inhalation. However, the direct effect of MITC on sensitive tissues of the eye is the predominant acute hazard. Eye irritation and odor complaints from agricultural applications of metam were responsible for designation of metam as a restricted use pesticide (CCR Titles 3 and 26, Section 6400).

7. Concentrations of MITC in air are somewhat uncertain because of the possible loss of MITC on the silica gel drying tubes placed in front of the charcoal trapping tubes in most of the exposure studies. Losses of MITC to the silica gel tubes were reported to be 58 to 100 percent for one sampling interval and 0 to 4 percent for another.

Health Effects

Humans

8. From a human exposure study designed to determine the eye irritation level for MITC (using special goggles to provide selective exposure to the eye region) a lowest-observed-adverse-effect-level (LOAEL) for eye irritation of 800 ppb was identified (Russell and Rush, 1996). The no-observed-adverse-effect-level (NOAEL) for eye irritation identified from this study was 220 ppb.

9. Other signs and symptoms of human acute and subacute exposure to MITC reported most frequently following the 1991 train derailment at the Cantara Loop that resulted in a large metam sodium spill in the Sacramento river included nausea, headache, throat irritation, dizziness, vomiting, and shortness of breath. Some patients also complained of chest tightness, cough, abdominal pain, diarrhea, and skin rash. Hyperventilation or anxiety-like symptoms including rapid breathing, tremulousness, and perioral and acrodigital paresthesias (tingling around the mouth and of the fingertips) were also noted.

10. Following an incident of agricultural drift over populated areas, residents of Earlimart, California were exposed to levels of MITC estimated to be in the range of 0.5 to 1.0 ppm (one-hour TWA). Odor complaints were received two hours after the initiation of the second day's application. Evacuation orders for residents located 0.45 to 0.6 miles away from the field were given based on "reports of symptoms," but the timing of the onset of symptoms or for the evacuation orders cannot be determined from the draft TAC. The following profile of symptomotology was compiled from: 1) interviews conducted six days after the incident, 2) complaints to the Tulare County Agriculture Department and Emergency Services, and 3) pesticide illness reports and medical records. Of 171 exposed individuals, nearly 80 percent experienced symptoms of eye or upper respiratory irritation (burning of the eyes, nose and/or throat). Non-specific systemic symptoms of headache, nausea, dizziness, shortness of breath, abdominal pain, vomiting, and weakness were present in approximately

60 percent of the cases. Sixteen percent had other respiratory complaints, including dyspnea, cough and/or exacerbation of pre-existing asthma.

11. Some exposures to MITC have exceeded the acute respiratory irritation level. Exposure to respiratory irritants can result in the development of prolonged adverse effects such as reactive airways dysfunction syndrome (RADS). In this condition, subsequent exposures to far lower levels of the same or another irritant gas will then trigger respiratory distress symptoms. This may be a hazard for MITC or combined MITC/MIC exposures.

Animals

12. Acute toxicity of MITC was studied in a variety of animal species including rats, mice, rabbits, dogs, cats, guinea pigs, and monkeys. Acute effects produced in laboratory animals following inhalation exposure included excitement, eye irritation, and dyspnea. Cats appear to be the most sensitive laboratory species. The NOAEL for irritation of the ocular mucosa in a four-hour exposure in this species was identified as 35 ppb (Nesterova, 1969). In rabbits, MITC was shown to be a severe skin and eye irritant. Studies in guinea pigs demonstrated that MITC is a strong dermal sensitizer.

13. Subchronic toxicity studies of MITC in laboratory animals provide information on adverse effects following inhalation, dietary, gavage, and dermal administration. In rats, adverse effects from inhalation exposure included mortality (at 467 ppm, or 1,400 mg/m^3 in a 24-day study), decreased body weight gain (at 84 ppm in a 24-day study), vascular effects in the lungs (at 0.37 ppm in a four-month study), and nasal discharge (at 45 ppm in a 12 to13 week nose only inhalation study). From the key 28-day inhalation study with Wistar rats, a LOAEL of 1.7 ppm was identified in the draft TAC document based on increased incidence of atrophy of the nasal olfactory epithelium in both sexes. MITC administered orally resulted in decreased feed consumption and body weight (in mice at 44 ppm in a three-week drinking water study and in a three-month gavage study), inactivity and abnormal feces (at 25 ppm in a ten-day gavage study in rats), forestomach acanthosis, hyperkeratosis, and submucosal cyst formation (at 3 ppm in an eight-month gavage study in rats), increased liver weight and liver inflammation, altered ovary and adrenal weight, and spermatogenic disorder (at 1 ppm in a three-month gavage study in mice), and blood changes (at 10 ppm in a three-month gavage study in mice). Subchronic dermal application of MITC produced skin ulceration, crust formation, neutrophil infiltration, enlarged peribronchial lymph nodes (at 120 ppm in a one-month dermal study in rats), and erythema and decreases in serum albumin and plasma cholinesterase activity (at 1 ppm in a 31-day dermal study in rats).

NOTE: PREVIOUS #14 WAS DELETED

14. Because of the small number of animals (five/sex/dose) and the high incidence of atrophy of the nasal olfactory epithelium in the controls (30 percent), the response at the two lowest dose groups (60 percent in either group) is not statistically significantly different from the controls. Therefore, it is difficult to definitively identify a LOAEL or NOAEL from the subchronic inhalation rat study. Accordingly, we applied benchmark dose methodology (BMD) to the data and identified the benchmark concentration at a response rate of five

percent (BMC_{05}) for use as a point of departure. Applying this methodology to the combined incidence data (total; focal plus non-focal atrophy), we derived a lower confidence limit on the BMC_{05} of 1.2 mg/m^3. Converting to ppm and adjusting for discontinuous exposure (experimental exposure was six hours/day, five days/week) a BMC_{05} of 70 ppb is calculated. We would adopt the adjusted BMC_{05} of 70 ppb as the reference point for the calculation of RELs and MOEs.

15. In long-term toxicity studies, MITC was administered via gavage (dogs) or drinking water (rats and mice). Adverse effects included decreased feed consumption and body weight along with poor condition in dogs (LOAEL of 2 mg/kg-day), and decreased water consumption and body weight in rats (LOAEL of 2.1 mg/kg-day) and mice (LOAEL of 9.82 mg/kg-day). Some blood and liver effects were observed in mice and dogs at higher doses (changes in blood platelets, total serum protein, hematocrit, and ratios of lymphocytes and neutrophils at 21.34 mg/kg-day in female mice and at 24.09 mg/kg-day in male mice and decrease of liver weights at 2 mg/kg-day in dogs). There is insufficient evidence of oncogenicity in any of the studies. No long-term study via inhalation is available.

16. There are two reproductive toxicity studies, one two-generation drinking water and one three-generation oral gavage study in rats. No reproductive effects were identified. Systemic effects observed at the mid and highest doses tested included decreased water consumption and weight loss at 10 and 50 ppm in the two-generation study and decrease of body weights in F_0 males at 3 and 10 mg/kg-day in the three-generation study.

17. Three developmental toxicity studies are available, one using rats and two using rabbits. These studies showed decreased fetal body weight and size at doses that also produced maternal adverse effects such as decreased feed consumption and body weight gain (at 25 mg/kg-day in rats, 5 mg/kg-day in New Zealand White rabbits, and at 3 and 10 mg/kg-day in albino rabbits). The maternal effects were noted in both species.

18. Most MITC genotoxicity data are negative. Evaluation of chromosomal effects in Chinese hamster V79 cells indicated a weakly positive response. There was no evidence for gene mutation in a mammalian cell assay. The results of microbial cell assays were considered not useful for hazard identification by DPR due to various deviations from Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) guidelines. Tests for sister-chromatid exchange (SCE) and DNA damage were negative.

19. Studies are available that were designed to evaluate MITC effects on the immune system, cardiovascular system, blood coagulation, hemolysis, and central nervous system. However, little can be concluded from these studies because only summary information was available for evaluation.

20. MIC is known to be highly reactive and acutely toxic to humans and animals. Acute symptoms following exposure to high air concentrations of MIC include skin and eye injuries, myelotoxicity, asthma, chest pain, pulmonary edema, dyspnea, respiratory failure, and death.

21. Positive genotoxicity data exist for MIC. Increased mutation frequencies were seen in L5178Y mouse lymphoma cells and SCEs and chromosomal aberrations were increased in Chinese hamster ovary cells exposed to MIC *in vitro*. Increases in SCEs and chromosomal aberrations were observed in bone marrow cells from $B6C3F_1$ mice exposed *in vivo*, and a dose-related increase in SCEs occurred in lung cells but not in peripheral blood lymphocytes. A significant increase in micronucleated polychromatic erythrocytes in the peripheral blood was also observed in male mice in one experiment. These data suggest that MIC could have carcinogenic potential.

Basis, Potency, and Range of Health Risks to Humans

22. The draft TAC document includes an assessment of risks from potential acute or short-term human exposures and from seasonal exposures to the airborne MITC following agricultural use of metam sodium, dazomet and/or metam potassium. The draft TAC document does not include an assessment of chronic health risks from potential chronic human exposures.

23. Human health risks are estimated in the draft TAC document from the acute or short-term exposures based on the eight-hour NOAEL of 220 ppb for eye irritation (Russell and Rush, 1996). This NOAEL was identified in an acute study with human volunteers and was used for calculating reference exposure levels (RELs) and margins of exposure (MOEs) for various groups. The NOAEL of 35 ppb for irritation of the ocular mucosa in a four-hour exposure in cats (Nesterova, 1969) was used in 1992 by OEHHA to calculate an acute REL for MITC following the Cantara Incident.

24. Both the human volunteer study (Russell and Rush, 1996) and the laboratory study in cats (Nesterova, 1969) have limitations for use in quantitative risk assessment. These limitations are listed in Table 1. While the use of the human study for eye irritation might be justified, it should be noted that an REL based on the NOAEL from the Nesterova (1969) study would be significantly lower, and the MOEs significantly less, than those calculated in the draft TAC document using Russell and Rush (1996).

25. The eye irritation endpoint used for evaluating acute human exposures to MITC was from a human volunteer study (Russell and Rush, 1996) where only the eyes were exposed (using goggles) to the material. In an actual exposure situation, in addition to the eyes, the nose and mouth would be simultaneously exposed, which may effectively lower the NOAEL for this endpoint. Uncertainty exists as to what degree the NOAEL would be affected.

26. RELs calculated in the draft TAC document for acute, seasonal and chronic exposures to MITC are presented in Table 2. The acute REL calculated from the human exposure study (Russell and Rush, 1996) is based on an eight-hour exposure. In the draft TAC document it is noted that because the level of eye irritation was unchanged at one, four and eight hours, the one, four, and eight-hour REL values are equivalent. Using the Russell and Rush (1996) study, the NOAEL for human eye irritation was 220 ppb after eight hours of exposure, based on subjective symptoms of eye discomfort at the next higher level of 800 ppb MITC. This NOAEL of 220 ppb is then divided by an uncertainty factor of ten (accounting for intra-species variability), resulting in an acute REL of 22 ppb (66 $\mu g/m^3$).

Table 1. Limitations of the Two Critical Experimental Studies for Acute MITC Exposure

Nesterova, 1969	Russell and Rush, 1996
1. Report lacks essential information on experimental conditions and parameters: • There is no information about the number of animals, sex, weight, or age of the three species reportedly used in the inhalation experiment. • No control groups were specified.	1. This study attempted to determine the human eye irritation threshold using an eye mask. It did not address MITC effects on the upper respiratory tract or other parts of the human body.
2. It is not possible to determine whether the toxic effects seen in experimental animals were based solely on MITC exposure: • The experimental method specified that MITC was generated from the decomposition of metam sodium promoted by heated soils. • Measurements of airborne MITC were undertaken, but no measurements were made of other volatile degradation products of metam sodium. • It is possible that toxic effects were due to the additive/synergistic effects of degradation products with MITC, or to MITC itself.	2. The recruitment questionnaire asked about medical history including eye infection/irritation, asthma, allergies, medication, smoking, and pregnancy. Subjects wearing contact lenses or pregnant and lactating women were excluded. However, the interim report did not indicate the number of subjects with these conditions who were included in the study. For example, the study may have excluded subjects with asthma or hay fever, as they may not have wanted to participate in a study involving chemical irritants. Therefore, only healthy, young adults may have been represented.
3. The quality or accuracy of the MITC assay method is not described. No information was provided about the nature of the airborne concentrations, whether they were consistent or variable, or when the measurements were undertaken.	3. The study included 138 human subjects (69 of each gender) recruited from the campus community, with a mean age of 32 (range of 18 to 67). These subjects did not represent the full age range nor, probably, the racial make-up of the California population.
4. The effects reported were primarily clinical observations. There was no evidence for an extensive toxicity evaluation as would be conducted under FIFRA guidelines. No organ weights or histology was reported, but some clinical chemistry and hematology apparently were done (no specific tests were identified and only the results were reported).	4. Lacrimation (tearing) may occur via the trigemino-facial reflex from either a direct (eye) or indirect (nasal) stimulation. By isolation of ocular from nasal exposure with the eye mask, the origin of the reaction can be differentiated. However, most individuals would experience full-face exposure to MITC with combined effects on nasal, eye, and upper respiratory nerve endings, and the skin. The study does not provide data to assess this likely exposure scenario.
	5. In animals, the Draize eye irritation test is evaluated using "irritation scores." In the human study, a non-invasive, subjective approach is used. Each test subject is asked to report on perceived eye irritation. Eye photographic analysis was found "not of value" because the more sensitive individuals "tended to be canceled out by others who displayed some native edema and redness in the early morning." It is unclear why this would not be useful, with each person acting as his or her own control, as stated. If this measure were applied properly, the results should have been more comparable to the animal irritation study method.

Table 2. Reference Exposure Levels for Acute, Seasonal and Chronic Exposures Calculated in the Draft TAC Document

Species	"NOEL"	REL
Acute Exposure (1, 4 or 8-hour)		
Human (adult)	220 ppb	22 ppb; 66 $\mu g/m^3$
Seasonal Exposure (24-hour)		
Rat	100 ppb	
Human		1 ppb; 3 $\mu g/m^3$
Chronic Exposure (24-hour)		
Rat	100 ppb	
Human		0.1 ppb; 0. 9 $\mu g/m^3$

27. In the draft TAC document both seasonal (subchronic) and chronic RELs were calculated (see Table 2). The seasonal REL of 1 ppb was calculated from the estimated subchronic NOAEL of 100 ppb. This estimated NOAEL was derived in the draft TAC document from the 28-day inhalation study LOAEL of 1.7 ppm (based on the increased incidence and severity of atrophy of the olfactory epithelium at this and the succeeding doses) by adjusting for discontinuous exposure by multiplying the LOAEL by an appropriate adjustment factor [1,700 ppb × (6/24 hours)] × (5/7 days) = 304 ppb]. This adjusted LOAEL was then divided by an uncertainty factor of 300 (a factor of three for LOAEL to NOAEL extrapolation, a factor of ten for inter-species, and a factor of ten for intra-species variability) to arrive at the seasonal REL of 1 ppb. A chronic REL of 0.1 ppb was derived by applying an additional uncertainty factor of ten to the subchronic NOAEL for subchronic to chronic exposure extrapolation.

NOTE: THE previous # 29 WAS REMOVED

28. Using the BMC_{05} of 70 ppb to calculate RELs would result in values of 0.7 ppb and 0.07 ppb for the subchronic and chronic RELs, respectively. The subchronic REL is calculated by applying a combined uncertainty factor of 100 (ten for inter-species extrapolation and ten for intra-species extrapolation) to the BMC_{05} of 70 ppb. The chronic REL is calculated similarly, with the application of an additional uncertainty factor of ten (total uncertainty factor of 1,000) to account for subchronic to chronic exposure extrapolation. Given the uncertainty in identifying a NOAEL or LOAEL from this study, the REL calculated using the

benchmark concentration might be more scientifically defensible than the REL calculated using the LOAEL.

29. The highest measured mean acute application site air concentration (one-hour exposure) was 2,853 ppb, resulting in a mean MOE of less than one. Nearly all (90 percent) of the MOEs for acute exposure to application site air were less than one. These estimates are well below an MOE of ten, which is generally considered by DPR to be protective of human health for adverse effects observed in human studies. Based on these considerations, acute exposures to MITC at application sites represent a public health concern and exposure to MITC in ambient air may pose a public health concern.

30. MOEs for acute exposure to average ambient air concentrations of MITC range from 15 to 2,200. MOEs of this magnitude are generally considered by DPR to be protective of human health for adverse effects observed in human studies. Based on these considerations, acute exposures to MITC at application sites represent a public health concern and exposure to MITC in ambient air may pose a public health concern.

31. MIC has been observed to cause reproductive toxicity (increased dead fetuses at birth) in Swiss mice after exposures to concentrations of 1 or 3 ppm for six hours/day during days 14 to 17 of gestation. A NOAEL was not observed in this study. DPR derived a NOAEL of 100 ppb from the LOAEL of 1 ppm using a LOAEL to NOAEL extrapolation uncertainty factor of ten; DPR considered this to be a six-hour ENOEL (estimated NOEL). DPR then calculated one-hour and 24-hour ENOELs of 600 ppb and 25 ppb, respectively, using a time extrapolation based on Haber's Law ($C^n \times T = K$, where C = concentration, T = time, K = a constant level or severity of response and n = an empirically-derived chemical-specific parameter greater than zero). The resulting ENOELs were then divided by an uncertainty factor of 100 to account for inter-species and intra-species variation, and corrected for the breathing rate of a child (0.76 m^3/kg-day) compared to that of a rat (0.96 m^3/kg-day). The resulting one-hour, six-hour and 24-hour acute RELs calculated for MIC by DPR were 7.6 ppb, 1.3 ppb and 0.3 ppb, respectively. OEHHA does not use time extrapolation in calculating acute RELs when the critical toxic effect is developmental toxicity (OEHHA, 1998). Using OEHHA methodology, an acute one-hour REL of 1 ppb (2.4 $\mu g/m^3$) can be calculated by dividing the NOAEL of 100 ppb by an uncertainty factor of 100 to account for inter-species and intra-species variation. Estimated air concentrations of MIC generated from the photolysis of MITC can be compared to this REL.

32. The estimated NOAEL used in the draft TAC document for evaluation of potential adverse health effects from seasonal exposures was 100 ppb based on increased incidence of atrophy of the nasal olfactory epithelium in both sexes in a 28-day rat inhalation toxicity study. The highest estimated mean seasonal ambient air concentration was 3.5 ppb in Weedpatch, Kern County during the summer of 1993. The corresponding MOE is 28. Three of fourteen MOEs for ambient exposure were less than 100, and, therefore, below the level generally accepted by DPR to be protective of human health for adverse effects observed in animal studies. Most MOEs for ambient exposures, however, were greater than 100, a level generally considered by DPR to be protective of human health for adverse effects observed in animal studies. Estimated mean seasonal application site air concentrations ranged from 2 to 80 ppb,

with corresponding MOEs ranging from 1 to 50. All MOEs for seasonal exposure to application site air were less than 100, and, therefore, below the level generally accepted by DPR to be protective of human health for adverse effects observed in animal studies. Based on these considerations, seasonal exposures to MITC at application sites represent a public health concern.

NOTE: PREVIOUS #35 WAS DELETED

33. Using the BMC_{05} to assess seasonal exposures, all seasonal MOEs for application-site exposures would be less than 100. MOEs for ambient air exposures would be less than 100 for 6 of 14 scenarios evaluated in the draft TAC document. Note that MOEs for 3 of 14 ambient air exposure scenarios were less than 100 using the estimated NOAEL (100 ppb) in the draft TAC document. Twice as many scenarios for exposure to MITC in ambient air have MOEs below the level generally considered by DPR to be protective of human health for adverse effects observed in animal studies when calculated based on the BMC_{05} instead of the estimated NOAEL used in the draft TAC document.

34. Based on the available information, seasonal exposure to MITC presents a public health concern. Because of the small numbers of animals used in the experiment and the uncertainties introduced into the risk assessment by estimating a NOAEL, the most scientifically defensible approach is to use BMD methodology to calculate the point of departure for assessing risks from seasonal exposures to MITC.

Uncertainties and Other Relevant Findings

35. Health risk assessment for acute inhalation exposure to MITC was based on a study involving human volunteers with their eyes exposed to air concentrations of MITC in a laboratory setting. In practice, people are most frequently exposed to airborne MITC following agricultural metam sodium applications. Under such conditions, inhalation exposure is not limited to MITC but also may include other degradation products such as CS_2, H_2S, and MIC. Uncertainty exists as to the degree of contribution of these products to the overall potential toxicity.

36. Potential health risks from chronic exposures to MITC have not been assessed because no chronic exposure data exist. The potential significance of repeated seasonal exposures to MITC is uncertain.

37. Uncertainty also exists as to the potency of MITC as a human dermal and pulmonary sensitizer. Potential sensitization properties of airborne MITC following metam sodium applications might also be enhanced due to MIC co-exposures.

38. No sensitive subpopulations have been specifically identified, although it has been observed that people with pre-existing respiratory conditions can be especially vulnerable to chemicals with respiratory irritant and sensitization properties (see finding above regarding RADS).

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August 7, 2002

Paul E. Helliker
Director
Department of Pesticide Regulation
1001 I Street
P.O. Box 4015
Sacramento, California 95812

Dear Mr. Helliker:

With this letter I am pleased to transmit to you the Scientific Review Panel on Toxic Air Contaminants' Findings on Metam Sodium and other Pesticidal Sources of Methyl Isothiocyanate. The findings were based on the Panel's review of the Department of Pesticide Regulation's draft report titled "Evaluation of Methyl Isothiocyanate (MITC) as a Toxic Air Contaminant."

The Panel reviewed the draft report as well as the scientific data on which the report is based, the scientific procedures and methods used to support the data, and the conclusions and assessments on which the report is based, as required by state law. The Panel also reviewed comments received and responses to those comments. In approving the report, it is the Panel's conclusion that the report, with the revisions requested by the Panel, is based on sound scientific knowledge.

The Panel recommends that you take the necessary regulatory steps to list methyl isothiocyanate as a toxic air contaminant. The Panel notes that methyl isothiocyanate is in the ambient air largely as a result of the breakdown of metam sodium, with smaller contributions from other pesticides such as metam potassium and dazomet. Therefore, the Panel also recommends that the Department of Pesticide Regulation take steps to regulate all pesticidal sources of methyl isothiocyanate. Finally, the Panel discussed and found that some breakdown products of metam sodium that are of concern, such as methyl isocyanate, are already considered toxic air contaminants under state law by already being listed as federal hazardous air pollutants. However, other breakdown products such as hydrogen sulfide are not listed, and should be identified as toxic air contaminants.

Let me also take this opportunity to thank the Department of Pesticide Regulation staff for their efforts in completing this report. The Panel appreciates the time and work that were put into the report as well as responding to further questions from the Panel.

Lastly, we ask that the Panel's findings and this letter be made a part of the final report.

Sincerely,

John R. Froines, Ph.D.
Chairman
Scientific Review Panel

cc: Scientific Review Panel members

Joan E. Denton, Ph.D., Director
Office of Environmental Health Hazard Assessment

Alan C. Lloyd, Ph.D., Chairman
Air Resources Board

Jim Behrmann
Liaison, Scientific Review Panel

Enclosure

Scientific Review Panel findings
on metam sodium and other pesticidal sources of methyl isothiocyanate
(The Department of Pesticide Regulation's document is entitled "Evaluation of methyl isothiocyanate (MITC) as a toxic air contaminant").

Use and Environmental Fate

1. Pesticidal use of MITC is infrequent in California, but MITC is the primary breakdown product and active principle of the highly used pesticide, metam-sodium. Agricultural use of metam-potassium and dazomet also produces MITC.

2. Nearly fifteen million pounds of metam-sodium were used in California in 1998, mainly for agricultural fumigation. The highest use occurs in Kern, Imperial and Fresno Counties. California use of metam-sodium more than doubled between 1990 and 1998.

3. Metam-sodium in soil is converted to MITC within the first 24 hours after application, depending on soil temperature and moisture. MITC diffuses through soil; a major portion is eventually lost by volatilization to air. Thus, while metam sodium is itself non-volatile, its application results in significant production and emission of air contaminants.

4. The half-life of MITC in air was reported as 29 to 39 hours in natural sunlight. MITC in air degrades by photolytic decomposition, in part to methyl isocyanate (MIC). MIC may be photochemically stable. Methyl isocyanide and N-methylformamide were identified as other possible breakdown products of MITC.

5. Metam-sodium decomposition can result in the formation of several other toxic chemicals including carbon disulfide (CS_2), methylamine, and hydrogen sulfide (H_2S). In practice, degradation to H_2S and MITC (and then to MIC) is favored.

6. Dazomet and metam potassium are two other pesticides registered for use as soil fumigants that produce MITC as the active agent. However, only 16,000 pounds of Dazomet and 9,200 pounds of metam-potassium were reported in 1998; metam sodium is the dominant agricultural source of MITC and MIC in California air.

Exposure associated with metam-sodium application

7. DPR's evaluation document summarizes six studies that measured airborne MITC at fields treated with of metam-sodium (application site studies). In two of these, the soil was sealed after application consistent with current label requirements. MITC measurements from the other four application site studies are presented as supporting data. The maximal air concentrations of MITC reported in the application studies may represent an upper-bound on exposure concentrations likely to be encountered immediately adjacent to metam-sodium treated fields in California. Three studies of MITC in ambient air in and near homes were described. While sampling in the ambient studies did not necessarily coincide with applications of metam-sodium in the area, the studies were carried out in high use areas of California. In one of the ambient studies, samples were mis-handled to the extent that the

data are not useful for exposure characterization.

8. DPR adjusted the measured air concentrations in all the exposure studies for field recovery percents (67-100%). Further, if the rate of metam sodium application was less than the maximum allowed, the resulting MITC concentrations were scaled linearly to the concentration that would be expected if the application had been at the maximal label-approved rate.

9. DPR computed short-term (1, 8, and 24 hour) air concentrations of MITC from measurements reported in the six application-site studies. Samplers were located from 5–970 meters from field edges. The highest one hour concentrations from each study ranged from 281-2853 ppb; the highest 24 hour concentrations (averaged from samples of shorter duration) range from 175-1102 ppb. Maximal measurements were taken just 5 meters from the field perimeter; inside current buffer zones.

10. Moderate-term (>2 day) air concentrations were computed for all application site studies by developing time-weighted averages for the measurements at each location over the length of the sampling period. The resulting values were used in margin-of-exposure (MOE) analysis of seasonal exposures.

11. MITC concentrations measured in ambient exposure studies were considerably lower than the concentrations adjacent to field applications. The two viable ambient studies produced moderate term air concentrations between 0.13-4.09 ppb, considerably lower than estimates of maximal seasonal exposures for people immediately adjacent to application sites. The Panel notes the limitations of the ambient air studies to represent actual population exposures in California's agricultural areas. Exposure is expected to vary considerably both temporally and spatially. The available data for MITC are insufficient for an adequate characterization of the distributions that underlie the observed variability in exposures.

12. Air concentrations of metam sodium breakdown products other than MITC were not determined in most exposure studies. However, a study by the Air Resources Board in Kern County in 1995 found application site concentrations of MIC from 0.09 to 2.5 ppb (12 hr. time-weighted average). Concurrent 12 hour measurements of MITC concentrations ranged from 0.08 to 84 ppb. H_2S concentrations up to 76 ppb were detected in samples collected from 1-4 hours post-application, in a monitoring study conducted by DPR in 1993.

13. Human exposure to atmospheric breakdown products of metam sodium can occur by both inhalation and dermal routes; the predominant exposure route is inhalation. No dermal toxicity endpoints were used in the risk appraisal.

Human Health Effects associated with Metam-Sodium Applications and Spills

14. A large spill of metam-sodium occurred in conjunction with a train derailment near Dunsmuir, California in 1991. As a consequence, the volatile breakdown products of metam-sodium were released into local air. The most frequently reported signs and

symptoms among those exposed were nausea, headache, throat irritation, dizziness, vomiting and shortness of breath. Exposure levels are uncertain, but have been estimated by modeling. Three different modeling approaches estimated peak concentrations within 100 meters of the spill at 650, 1300, and 4500 ppb.

15. One report documented cases of persistent irritant-induced asthma and exacerbation of asthma in persons exposed to metam-sodium breakdown products as a result of the Dunsmuir spill. Exposure to respiratory irritants, such as MITC and MIC, can cause prolonged adverse effects including reactive airways dysfunction syndrome (RADS), a form of chemically-induced asthma.

16. Excluding the Dunsmuir incident, 390 case reports associated with metam-sodium applications were received by the California Pesticide Illness Surveillance Program between 1990 and 1999. Ocular signs and symptoms included watery, burning and itchy eyes and blurred vision. Systemic signs and symptoms included nausea, diarrhea, weakness, dizziness, headache, and vomiting. Respiratory signs and symptoms included cough and shortness of breath.

17. An application of metam sodium in Earlimart, California in 1999 caused 173 individuals, including 2 emergency response personnel, to report exposure-related illness. Neighborhood evacuations fear and medical expense also contributed to a considerable impact on the community. Irritation of the eyes, nose and/or throat was noted in the majority of complaints. There were 5 cases of asthma exacerbation and 23 people with dyspnea, chest pain and/or cough. 8 cases of rash were identified. Exposure levels are unknown. Air dispersion modeling by DPR estimated that the majority of those who filed odor complaints or reported illness were likely exposed to a 1-hour time-weighted average (TWA) concentration between 0.5 and 1 ppm. Adjacent to the field, 1 hour TWAs were estimated to be 3 ppm. Modeling, while highly uncertain, also suggests that some illness could have occurred at 1 hr. TWA concentrations below 0.5 ppm, near the experimentally defined NOEL for MITC. Exposure to other breakdown products of metam sodium was not modeled, and it is not known to what extent MITC and/or other products contributed to illness in Earlimart. Whether exposure to the suite of breakdown products can cause illness at MITC levels that would not induce effects in the absence of the other compounds remains an important question for risk management of metam sodium (see findings # 44 and 45, below.)

Exposure of Experimental Animals to Metam-Sodium in Drinking Water

18. Metam-sodium in aqueous solution produces MITC. Therefore, drinking water administration of metam-sodium to laboratory animals may provide data relevant to the toxicological evaluation of MITC in air. The available drinking water studies did not, however, quantify the MITC present in metam-sodium treated water.

19. Subchronic exposure of mice and rats to metam-sodium in drinking water produced decrements in body weight gain, food consumption and water intake. These findings are similar to results noted in MITC treated animals (finding #24).

20. Chronic exposure to metam-sodium via drinking water produced angiosarcomas in male mice and rats; the draft TAC evaluation document did not provide detailed data.

Human Health effects of MITC exposure

21. One controlled exposure experiment with MITC in humans has been conducted to date. Increased blink rate and irritation, as measured on a subjective scale, were observed during exposures to 0.8, 1.9, and/or 3.3 ppm MITC. Whether effects were observed at a particular exposure level depended upon the duration of exposure. No significant effects were observed in groups of subjects exposed to 220 ppb MITC for 4 or 8 hours. In all experiments, exposure was to the eyes only; respiratory irritation could not be evaluated.

22. Two clinical reports suggest that MITC could cause dermal reactions in humans, consistent with limited evidence of skin rash from the Earlimart incident (finding #17).

Exposure of Experimental Animals to MITC

23. Acute toxicity of MITC has been studied in a variety of animal species including rats, mice, rabbits, dogs, cats, guinea pigs and monkeys. Acute effects in rats following inhalation exposure included hyperactivity, hypoactivity, eye irritation and increased respiratory rate. In rabbits, MITC was shown to be a severe skin and eye irritant. MITC may be a dermal sensitizer in guinea pigs, in agreement with limited evidence in humans (finding #22).

24. Adverse effects have been reported in subchronic toxicity studies of MITC in laboratory animals following inhalation, gavage or dietary, and dermal administration. Effects noted in a 4 week inhalation exposure in rats included nasal epithelial atrophy at all exposure levels tested, with increased pathology of the respiratory tract at the highest exposure. Effects observed at the highest concentration of 34 ppm included bronchopneumonia, epithelial proliferation, rhinitis, tracheal necrosis, and squamous metaplasia. In a 90 day inhalation study in rats, effects included decreased body weight gain, decreased food consumption, nasal discharge, decreased serum protein and mortality; histopathological examination was not performed in the 90 study.

25. Chronic oral toxicity studies of MITC have been conducted in dogs, rats and mice; no chronic studies of inhalation exposure were identified. A suggestion of oncogenic potential was noted in rats and mice exposed to MITC in drinking water. In female rats given 2, 10 or 50 ppm of MITC in the drinking water for 104 weeks, the incidence of benign and malignant mammary gland tumors was significantly higher in the 10 ppm, but not in the 2 or 50 ppm groups. A comparison of controls versus all MITC exposed animals did not show a statistically significant increase in overall tumor incidence. In the mouse drinking water study, a small increase in cutaneous fibrosarcomas was observed in the highest dose group of both males and females. When the data from both sexes are combined, the increase in tumor incidence (from 0% to 4.3%), is statistically significant ($p<0.05$). In conclusion, there is a suggestion of animal carcinogenicity, but the data are inadequate and further investigation is required.

26. MITC has been tested for genotoxicity in microorganisms, cultured mammalian cells and laboratory rodents. Most study results were negative. A technically limited evaluation of chromosomal effects in Chinese hamster V79 cells indicated a weakly positive response.

27. No reproductive effects were identified in a two-generation drinking water study in rats or in a three-generation oral gavage study in rats. Mild systemic effects observed included decreased water consumption and occasional decrements in weight gain compared to untreated animals. In a 3 month oral gavage study in mice and rats, mild decrements in spermatogenesis and decreased ovary weights were noted in both species.

28. Three developmental toxicity studies were reviewed, one in rats and two in rabbits. These studies showed decreased fetal body weight and size at doses that also produced maternal adverse effects such as decreased feed consumption and body weight gain. The maternal effects were noted in both species.

Health Effects of MIC

29. MIC is highly toxic. Accidental release of 30 to 35 tons of MIC from a pesticide factory in Bhopal, India, caused thousands of deaths by acute respiratory failure. Survivors suffered skin and eye injuries, shortness of breath, chest pains, cough, throat irritation, choking and hemoptysis (expectoration of blood). Objective signs of the corrosive effects of MIC on the respiratory tract were interstitial and alveolar edema and destructive lung lesions with cavitation, alveolar wall thickening and interstitial fibrosis. Pulmonary function tests indicated lung volume, air flow and pulmonary vascular impairments. Bronchiolitis obliterans was a long term result of the acute lung injury. MIC exposure concentrations in the Bhopal accident were estimated to be between 13 and 100 ppm. Many of the acute and chronic signs observed in humans have been reproduced in experimental laboratory experiments (mice and rats).

30. In three controlled exposures of human volunteers to MIC, eye irritation and lacrimation were observed after exposures ranging from 0.5 ppm to 5 ppm for10 seconds to 50 minutes.

31. MIC exposure has severe consequences for fetal and neonatal survival. In Bhopal, fetal loss rose from an estimated normal incidence rate for that area of 6-10%, to 43% in the exposed population. Mortality among infants exposed *in utero* increased over four-fold, from 2.6-3% in the 30 days after birth during the 2 years preceding the accident, to 14% after the disaster. Animal data support this finding: pregnant mice exposed to 1 ppm MIC for 6 hours/day on gestation days 14-17 had a 3.3% fetal mortality rate, compared to 0.4% in controls.

32. MIC has tested positive in several assays for genotoxicity, including tests for chromosomal damage and point mutation, *in vitro* and *in vivo*. In Bhopal survivors, chromosomal aberrations in peripheral lymphocytes were noted 2.5 months after the accident. The findings of clastogenicity and genotoxicity suggest that MIC could have oncogenic potential. However, in the only oncogenicity study identified, mice were exposed for just two hours, which did not result in tumor production. Whether MIC is oncogenic remains unknown.

Health Effects of Other By-Products of Metam Sodium Use

33. Brief summaries of the toxicity of hydrogen sulfide, carbon disulfide, methylamine, and carbonyl sulfide are provided in the TAC evaluation. Based on the limited available exposure information, H_2S poses the greatest exposure concern of these compounds. H_2S is a highly toxic, irritant gas that causes respiratory symptoms and eye irritation after acute exposure. At high concentration it paralyzes the sense of smell. Airborne concentrations of 700 ppm and more cause immediate death through cytotoxic asphyxia.

Human Health Risks

34. Risks of exposure to metam-sodium were not assessed for this document because metam sodium is not present in air after agricultural use.

35. Eye irritation in human volunteers was chosen as the critical endpoint for acute exposure to MITC. DPR identified an acute lowest observed adverse effect level (LOAEL) for eye irritation of 800 ppb and an acute no observed adverse effect level (NOAEL) of 220 ppb.

36. A subchronic LOAEL of 1.7 ppm MITC was identified from a 4 week inhalation study in rats, based on increased atrophy of the nasal epithelium in exposed animals compared to controls. A subchronic NOAEL of 100 ppb was estimated from the LOAEL by adjusting to continuous exposure and applying an uncertainty factor of 3. Benchmark dose analysis of the dose-response data yields similar results.

37. Margins of exposure (MOEs) for acute exposures to MITC near field applications of metam-sodium were computed as the ratio of the NOAEL for eye irritation to observed air concentrations. Because the ratio in this case involves an effect level derived from a human study, a MOE of at least 10 beyond the no-effect level is considered to be protective; MOEs less than 10 indicate risk. Using the maximal exposure levels reported in application site studies, acute MOEs ranged from <1 to 17; all but 2 MOEs were less than 10. The acute exposures as measured thus indicate potential risk of eye irritation to bystanders.

38. MOEs for seasonal exposures at application sites were computed as the ratio of the subchronic NOAEL (finding #36) to moderate-term air concentrations (after adjustment to 23/120 days. Because these ratios compare human exposure to no effect levels in animals, a MOE must be at least 100 to be considered protective. The MOEs for seasonal exposure ranged from 1-50, indicating potential risks to those exposed at metam-sodium treated fields on a repeated basis during the season of use.

39. Reference exposure levels (REL) for acute, seasonal and chronic exposures developed by DPR are in Table 1. . Because toxicological data on chronic inhalation exposure to MITC are lacking, DPR's chronic REL was based on the NOAEL for nasal epithelial atrophy estimated from the 28 day inhalation study in rats.

Table 1. NOAELs and RELs for acute, seasonal and chronic exposures to MITC

Species	NOAEL	REL
Acute Human	220 ppb	22 ppb
Seasonal (subchronic) Rat Human	100 ppb (estimated from LOAEL)	 1 ppb
Chronic Rat (subchronic study) Human	100 ppb (estimated from LOAEL)	 0.1 ppb

40. DPR developed a NOAEL and REL for acute exposure to MIC. A LOAEL of 500 ppb for a 10 minute exposure was selected from the three available studies of human eye irritation (finding #30). This yielded an acute REL of 0.98 ppb.

41. The highest MIC concentration measured after application of metam-sodium in the one available data set was 2.5 ppb (12 hour sample), exceeding the one hour REL of 0.98 ppb. The concentration of MITC during the same period was 67 ppb. Since all six studies of metam-sodium application reported maximum 24-hour MITC levels higher than 67 ppb (finding #9), MIC may have been present in concentrations greater than 2.5 ppb as well. While DPR did not carry out an MOE analysis for MIC due to very limited data, these results suggest a potential risk associated with acute exposures. It is important that greater effort be directed to determining levels of MIC present in air after application of metam sodium so that overexposure to this highly toxic compound can be avoided.

42. Concentrations of hydrogen sulfide related to metam-sodium applications were measured in only one of the available studies. The report noted that the highest measured concentration, 76 ppb, is more than twice the California Ambient Air Quality Standard of 30 ppb. There is a need for better data and control of exposure at metam-sodium treated fields, similar to that noted for MIC.

Uncertainties and Other Relevant Findings

43. Little is known about the variability in human inhalation exposures to pesticides and their breakdown products. How representative the exposure studies reported here are for other locations with metam-sodium use is not known. Distributions of ambient exposures are particularly complex and difficult to characterize with currently available data.

44. Following agricultural metam-sodium applications, inhalation exposure is not limited to MITC, but may also include other degradation products such as CS_2, H_2S and MIC. There is uncertainty about how these breakdown products interact to produce the overall potential toxicity deriving from the use of metam-sodium, but MITC, MIC and H_2S have all been

associated with ocular and respiratory irritation. DPR concluded that, while there are no data to address mixed exposure, additive or synergistic effects of MITC, MIC and H_2S in respiratory and ocular tissues are plausible. If both the modeled exposure estimates for MITC in Earlimart (finding #17) and the experimentally derived NOEL for MITC (220 ppb) are accurate, then some illnesses in Earlimart may have been produced at MITC concentrations near the NOEL because of exposure to the mixture of breakdown products.

45. The limited data available indicate that MIC and H_2S concentrations may exceed benchmark risk levels during applications of metam sodium. However, most exposure studies assessed only MITC concentrations. Risk assessment of metam sodium use based only on MITC may significantly underestimate human health risks. The combined risk of exposure to the mixture of irritants is the most relevant benchmark by which risk management strategies for metam sodium should be measured. To adequately characterize the risk resulting from a metam sodium application, exposure data for all toxic breakdown products is necessary. Further air monitoring studies to assess exposures resulting from metam-sodium application are needed, and should include assessment of MITC, MIC and H_2S.

46. Potential health risks from chronic exposures to MITC remain uncertain. MITC may have oncogenic potential, as discussed above in finding #25. The possibility of oncogenicity suggested by the MITC data is supported by the observation that tumors were produced in drinking water studies with metam-sodium. Clear genotoxicity of MIC, which is produced metabolically from MITC, is additional supporting evidence. There is an overall consistency in the data across these three compounds that suggest a potential cancer risk from metam-sodium use.

47. The potency of MITC as a dermal and pulmonary sensitizer in humans is uncertain. Sensitization by MITC following metam sodium applications might also be enhanced by co-exposures to MIC and other irritants.

48. No sensitive sub-populations have been specifically identified for metam-sodium by-products, although it has been observed that people with pre-existing respiratory conditions can be especially vulnerable to chemicals with respiratory irritant and sensitization properties.

Conclusions

49. DPR regulations (Code of California Regulations, Title 3, Section 6890(b)) specify that if pesticide air concentrations exceed levels that would result in a 10-fold lower risk than those determined to constitute a negligible risk, then the pesticide shall be identified as a Toxic Air Contaminant. Such is the case for MITC, based on the MOEs for acute and seasonal exposure at application sites.

50. The Panel has reviewed the draft version of the DPR report, "Evaluation of Methyl Isothiocyanate (MITC) as a Toxic Air Contaminant" as well as the scientific procedures and methods used to support the data, the data itself and the conclusions and assessments on which the report is based. The Panel has also reviewed and considered public comments

including those submitted by the Metam Sodium Task Force, and agency responses to comments. The Panel concludes that the report, with the revisions specified by the SRP, is based upon sound scientific knowledge, and represents a balanced assessment of our current scientific understanding.

51. The Panel recommends that the Director of DPR initiate regulatory steps to list MITC as a Toxic Air Contaminant pursuant to FAC §14023(d). In addition, because MITC in air derives overwhelmingly from applications of metam sodium, with a smaller part contributed by metam potassium and dazomet, we recommend that these three pesticides be listed as TACs. Other pesticides, not noted in this document, that break down to MITC should also be identified as TACs. Other breakdown products resulting from metam sodium use must also be considered. MIC and CS_2 are automatically listed as TACs due to their status as Hazardous Air Pollutants. Hydrogen sulfide should be identified as a TAC, based on its known toxicity and release as a breakdown product of metam sodium.

I certify that the above is a true and correct copy of the findings adopted by the Scientific Review Panel on April 26, 2002.

John R. Froines 8/8/02

John R. Froines, Ph.D.
Chairman
Scientific Review Panel

dpr

Department of Pesticide Regulation

Paul Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

MEMORANDUM

TO: Paul H. Gosselin
Chief Deputy Director

FROM: Paul E. Helliker Paul Helliker
Director
(916) 445-4000

DATE: August 21, 2002

SUBJECT: DIRECTOR'S PROPOSED DECISION CONCERNING METHYL ISOTHIOCYANATE AS A TOXIC AIR CONTAMINANT

Attached is a public notice of the proposed decision concerning my response to the Scientific Review Panel's findings on methyl isothiocyanate as a toxic air contaminant. My response has been made in accordance with all authorities and requirements stipulated in the Food and Agricultural Code and California Code of Regulations that mandate this determination. The Scientific Review Panel's findings were transmitted to me on August 14, 2002. Therefore, my response has been made within the 10-day statutory deadline.

I thank you, staff, and all the members of the Scientific Review Panel for the excellent work.

Attachment

cc: Alan Lloyd, ARB, Chair (w/Attachment)
Joan Denton, OEHHA, Director (w/Attachment)
Scientific Review Panel (w/Attachment)
Tobi Jones, Assistant Director (w/Attachment)
Douglas Y. Okumura, Assistant Director (w/Attachment)
Chuck Andrews, Chief (w/Attachment)
Barry Cortez, Chief (w/Attachment)
David Duncan, Chief (w/Attachment)
Gary Patterson, Chief (w/Attachment)
Scott T. Paulsen, Chief (w/Attachment)
John Sanders, Ph.D., Chief (w/Attachment)

dpr

Department of Pesticide Regulation

Paul Helliker
Director

Gray Davis
Governor

Winston H. Hickox
Secretary, California Environmental Protection Agency

Post Until
September 27, 2002

NOTICE OF PROPOSED DECISION CONCERNING THE DIRECTOR'S DECLARATION OF METHYL ISOTHIOCYANATE (MITC) AND OTHER PESTICIDES THAT GENERATE MITC AS TOXIC AIR CONTAMINANTS

Section 14023 of the Food and Agricultural Code (FAC) requires the Director of the Department of Pesticide Regulation (DPR) to determine if a pesticide is a toxic air contaminant (TAC) after receiving the findings of the Scientific Review Panel (SRP), a panel of experts representing a range of scientific disciplines. Based on the findings of the SRP's assessment of the report entitled, "Evaluation of Methyl Isothiocynate as a Toxic Air Contaminant," and the criteria given in Title 3, California Code of Regulations (CCR) section 6890(b), the Director proposes to declare Methyl Isothiocyanate (MITC) and other pesticides that generate MITC as TACs.

Background

With the enactment of California's Toxic Air Contaminant Act (Assembly Bill 1807, Tanner, Chapter 1047, Statutes of 1983; amended by Tanner, Chapter 1380, Statutes of 1984), the Legislature created the statutory framework for the evaluation and control of chemicals as TACs. The statute defines TACs as air pollutants that may cause or contribute to increases in serious illness or death, or that may pose a present or potential hazard to human health. DPR is responsible for the evaluation of pesticides as TACs.

In general, the law focuses on the evaluation and control of pesticides in ambient community air. In implementing the law, DPR must: (1) conduct a review of the physical properties, environmental fate, and human health effects of the candidate pesticide; (2) determine the levels of human exposure in the environment; and (3) estimate the potential human health risk from those exposures. The law requires DPR to list in regulation those pesticides that meet the criteria to be TACs.

For each pesticide, the law requires the preparation of a report that includes: the environmental fate and use of the pesticide, an assessment of exposure of the public to air concentrations of the pesticide, and a health assessment. The report is reviewed by the Office of Environmental Health Hazard Assessment and the Air Resources Board, and is made available for public review. Based on the results of these reviews, the draft report is revised as appropriate. The draft undergoes a rigorous peer review for scientific soundness by the SRP. Based on the results of this comprehensive evaluation, the DPR Director determines whether the candidate is a TAC. If the Director determines the pesticide meets the criteria to be a TAC, DPR declares the pesticide a TAC in regulation, and adds it to the TAC list.

Once a candidate pesticide has been declared a TAC, it enters phase two of the program--the mitigation, or control, phase. In the mitigation phase, DPR investigates the need for, and appropriate degree of, control for the TAC. If reductions in exposure are needed, DPR must develop control measures to reduce emissions to levels that adequately protect public health.

Department Conclusions

Title 3, CCR section 6890 states, "A pesticide shall be identified as a toxic air contaminant if its concentrations in ambient air are greater than the following levels (for the purposes of this section, a threshold is defined as the dose of a chemical below which no adverse effect occurs):

(a) For pesticides which have thresholds for adverse health effects, this level shall be ten-fold below the air concentration which has been determined by the Director to be adequately protective of human health.

(b) For pesticides which do not have thresholds for adverse health effects, this level shall be equivalent to the air concentration which would result in a ten-fold lower risk than that which has been determined by the Director to be a negligible risk."

DPR expresses risk as the margin of exposure (MOE), the ratio of the no observable effect level (NOEL) to the air concentration. DPR considers an MOE of ten adequate to protect humans if the NOEL is derived from human data. This takes into account the possibility of ten-fold variations in susceptibility within the human population. DPR considers an MOE of 100 adequate to protect humans when the NOEL is determined in animals. This accounts for an additional ten-fold uncertainty between laboratory animals and humans, and assumes that humans are more sensitive than animals. Therefore, according to the criteria established in regulations, pesticides with an MOE less than 100 or 1,000 if the NOEL is derived from human or animal data, respectively, should be identified as TACs.

Using the critical acute NOEL of 220 parts per billion (ppb) established in a human eye irritation study, and the short-term ambient exposure levels, MITC acute ambient MOEs ranged between 15 and 2200, and meet the criteria (MOE <100) for identifying a TAC. Under the short-term application site exposure scenarios, the MOEs for 1-, 8-, and 24-hour exposures were <1 to 5, <1 to 7, and <1 to 17, respectively, also meeting the criteria for identifying a TAC.

Using the critical estimated subchronic NOEL of 100 ppb established in the four-week rat inhalation study and the ambient exposure levels mean seasonal ambient MOEs ranged between 28 and 166,667, meeting the criteria (MOE <1000) for identifying a TAC. Under seasonal application site exposure scenarios, the MOEs ranged between 1 - 50, also meeting the criteria for identifying a TAC.

The SRP agrees with the science presented in the report and recommends that the Director identify MITC and all pesticidal sources of MITC as TACs. The SRP also recommends listing other metam sodium breakdown products, such as hydrogen sulfide, as TACs, if not already designated.

The law (FAC section 14021) and regulations (Title 3, CCR section 6890) defines TACs as pesticides. Breakdown products are not defined as pesticides in the law or regulations, so DPR lacks legal authority to list hydrogen sulfide and other metam sodium breakdown products as TACs. However, DPR can control exposure to the breakdown products by regulating the parent compound.

Department Actions

DPR proposes to adopt a regulation designating MITC and other pesticides that generate MITC as TACs. DPR proposes to add MITC and other pesticides that generate MITC to the list of pesticides in Title 3, CCR section 6860(a).

Although metam sodium is not specifically listed as a TAC, it is one of the pesticides that generate MITC. DPR will regulate it as a precursor to MITC, and the potential effects from the other metam sodium breakdown products will be considered in managing the risks.

DPR will conduct a public hearing concerning the proposed regulation.

APPROVED BY: Paul Helliker Date: 8/23/02
Paul Helliker, Director